Chapter 18
Multiple Myeloma

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Introduction

Multiple myeloma (MM) is characterized by the proliferation of monoclonal plasma cells in the bone marrow and usually the presence of a monoclonal protein in the serum and/or urine. Secondary end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone destruction (CRAB criteria) indicates symptomatic disease requiring therapy [1]. Furthermore, the presence of an abnormal serum free light chain ratio (>100, with involved free light chains >100 mg/l), two or more focal lesions in MRI or PET/CT as well as more than 60% monoclonal plasma cells in the bone marrow are myeloma-defining events according to the International Myeloma Working Group guidelines [2]. The introduction of novel agents and monoclonal antibodies revolutionized the treatment of MM in the last years and with every new

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drug approval, the value of ongoing utilization of autologous stem cell transplantation (ASCT) is questioned. However, recent phase III trials confirmed that combining novel agents with ASCT is associated with longer progression-free survival (PFS) compared to treatment with novel agents alone (Table 18.1) [3–6]. Although MM is still considered to be an incurable disease, long-lasting remissions over 10 years can be achieved making it difficult to determine if overall survival can serve as a primary endpoint for trials [7]. Furthermore, the outcome varies significantly among newly diagnosed patients based on risk stratification (Table 18.2) [8].

Table 18.1 Phase III studies comparing treatment with novel agents in combination with ASCT to treatment with novel agents alone

Study	*n*	Control arm	PFS (median in months)	*p*	OS	*p*
Palumbo et al., NEJM, 2014 [3]	273	MPR	43.0 vs. 22.4	$p < 0.001$	4-year OS: 81.6% vs. 65.3%	$p = 0.02$
Gay et al., Lancet Oncol, 2015 [4]	256	RCD	43.4 vs. 28.6	$p < 0.0001$	4-year OS: 86% vs. 71%	$p < 0.004$
Attal et al., NEJM, 2017 [5]	700	VRD	50 vs. 36	$p < 0.001$	4-year OS: 81% vs. 82%	Not significant
Cavo et al., ASH, 2016 [6]	1192	VMP	nr vs 44	$p = 0.002$	3-years OS: 85% vs. 85%	Not significant
Gay et al., ASCO, 2019 [86] Abstract 8002	474	KRD	Odds ratio 0.42[a]	$p = 0.021$	na	na

MPR melphalan, prednisone, lenalidomide; *RCD* lenalidomide, cyclophosphamide, dexamethasone; *VRD* bortezomib, lenalidomide, dexamethasone; *VMP* bortezomib, melphalan, prednisone; *nr* not reached; *na* not available
[a]Odds ratio in multivariate analysis

Table 18.2 International Staging System (ISS) and revised-ISS [8]

ISS stage	*Criteria*	*5-year PFS (%)*	*5-year OS (%)*
I	β_2-microglobulin < 3.5 mg/l Albumin ≥ 35 g/l	49	77
II	Not ISS I or ISS III	36	62
III	β_2-microglobulin ≥ 5.5 mg/l	30	47
Revised-ISS stage	*Criteria*	*5-year PFS (%)*	*5-year OS (%)*
I	ISS I Standard risk cytogenetics[a] LDH within normal range[b]	55	82
II	Not R-ISS I or R-ISS III	36	62
III	ISS III High-risk cytogenetics *AND/OR* LDH above the normal range	24	40

PFS progression-free survival, *OS* overall survival
[a]High-risk cytogenetics – del(17p) and/or t(4;14) and/or t(14;16)
[b]*LDH* lactate dehydrogenase

Assessment of Transplant Eligibility

There is no formal age cut-off for transplant eligibility in MM. Most phase III trials of ASCT have enrolled patients with an upper age limit of 65 years but other trials such as BMT CTN 0702 and CALGB 100104 allowed enrollment to 70 years of age. ASCT can be performed safely in older, medically fit patients [9, 10]. Therefore, transplant eligibility should be determined mostly on the basis of comorbidities. Table 18.3 summarizes the recommended assessments prior to ASCT at Roswell Park Comprehensive Cancer Center.

Table 18.3 Recommended assessments prior to ASCT

Examination/assessment	Time prior to ASCT
Physical examination	At admission
Blood test: Complete blood count including differential blood count Comprehensive metabolic panel (glucose, BUN, creatinine, sodium, potassium, calcium, liver function tests) Liver function tests (bilirubin, ALP, SGOT, SGPT, GGT) CRP, TSH, b-HCG (premenopausal) Coagulation tests (INR, PTT) Urinalysis (urine sediment, creatinine clearance in 24 h urine collection)	30 days
Viral serology Hepatitis B (HBsAG, anti-HBc) Hepatitis C (anti-HBC) HIV (antibodies against HIV1+2) Treponema pallidum (IgG/IgM) HSV1, HSV2, and VZV (IgG/IgM)	30 days
Central blood cultures of implanted port (aerobic and anaerobic)	30 days
Cardiopulmonary function: ECG Echocardiography Pulmonary function test (CO diffusion capacity, BGA)	30 days
Menstruation prophylaxis in premenopausal patients	Start 4 weeks prior to admission
Optional Contact blood bank if Daratumumab prior to ASCT (incorrect cross-match testing possible) HLA-antibodies (matching platelet concentrate necessary) Chest CT scan Rectal swab for MDRO screening	Prior to admission

BUN blood urea nitrogen, *ALP* alkaline phosphatase, *SGOT* serum glutamic oxaloacetic transaminase, *SGPT* serum glutamate pyruvate transaminase, *GGT* gamma-glutamyl transferase, *CRP* C-reactive protein, *TSH* thyroid-stimulating hormone, *b-HCG* beta-human chorionic gonadotropin, *MDRO* multidrug-resistant organism

Induction Therapy

The common practice of bortezomib-based induction therapies is supported by large meta-analyses [11]. Recent phase III trials compared different combination partners for bortezomib (Velcade®) during induction therapy before ASCT.

1. The initial EVOLUTION phase I/II study appeared to demonstrate that VCD (bortezomib, cyclophosphamide, and dexamethasone) and VRD had similar outcomes [12].
2. The German GMMG MM5 trial showed that VCD (bortezomib, cyclophosphamide, and dexamethasone) is less toxic than PAd (bortezomib, doxorubicin, and dexamethasone) [13].
3. The French IFM2013-04 trial demonstrated higher rates of high-quality responses for VTD compared to VCD [14].
    a. However, VTD was associated with higher rates of neuropathy compared to VCD.
    b. Although there has never been a direct prospective, randomized comparison between VTD and VRD (bortezomib, lenalidomide, and dexamethasone), many centers utilize VRD as recently applied in the IFM/DFCI2009 phase III trial [5].
4. Currently, second-generation novel agents such as ixazomib (Ninlaro®) (in combination with lenalidomide and dexamethasone [IRD]) [15] and carfilzomib (Kyprolis®) (in combination with lenalidomide/dexamethasone [KRD] or cyclophosphamide/dexamethasone [KCD]) [16] are being tested as induction before ASCT with promising results.
5. The CASSIOPEIA trial investigating VTD with or without daratumumab (Darzalex®) before and after ASCT showed for the first time superiority of an induction regimen incorporating a monoclonal antibody [17].
6. Further results from trials incorporating monoclonal antibodies such as elotuzumab (Empliciti®) and isatuximab (e.g., Clinicaltrials.gov identifier NCT03617731) into induction therapy before ASCT are expected in 2019/2020.
7. Table 18.4 summarizes recent phase II/III trials on induction therapy before ASCT.

Stem Cell Mobilization

An adequate collection of mobilized peripheral stem cells is a crucial or successful outcome of autoHCT. A dose of $>2 \times 10^6$ CD34+ cells/kg is considered the minimum target dose to achieve optimal engraftment [18]. The main risk factors for poor mobilization are age >60 years, thrombocytopenia [19], extensive previous treatment with radiotherapy or alkylating agents [18, 20–23], and prolonged use of lenalidomide [24–27]. Stem cell mobilization can be performed with growth factors alone, a combination of growth factors with chemotherapy, or with chemokine receptor antagonists (Table 18.5).

Table 18.4 Summary of most common induction therapies before ASCT in recent phase II/III trials

Study	Regimen	Drugs	Common adverse events		% ≥VGPR
Mai et al., Leukemia, 2015 (n = 501), Phase III [11] Intravenous bortezomib n = 304 Subcutaneous bortezomib n = 197	Pad	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Doxorubicin 9 mg/m^2, d 1–4 Dexamethasone 20 mg/d, d 1–4, 9–12, 17–20 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	25% 15% 6% 3% (all ≥ II)	34% after 3 cycles
	VCD	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Cyclophosphamide 900 mg/m^2, d 1 Dexamethasone 40 mg/d, d 1, 2, 4, 5, 8, 9, 11, 12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	22% 8% 3% 2% (all ≥ II)	37% after 3 cycles
Moreau et al., Blood, 2016 (n = 385), Phase III [14, 15] Subcutaneous bortezomib	VCD	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Thalidomide 100 mg/d Dexamethasone 40 mg/d, d 1–4, 9–12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	10% 3% 2% 0% (all ≥ III)	56% after 4 cycles
	VTD	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Cyclophosphamide 500 mg/m^2, d 1, 8, 15 po Dexamethasone 40 mg/d, d 1–4, 9–12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	8% 8% 2% 1% (all ≥ III)	66% after 4 cycles
Attal et al., NEJM, 2017 (n = 700), Phase III [5] Intravenous bortezomib	RVD	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Lenalidomide 25 mg/d, d 1–14 Dexamethasone 20 mg/d, d 1, 2, 4, 5, 8, 9, 11, 12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	9% 12% 4% (all ≥ III) Not reported	46% after 3 cycles

(continued)

Table 18.4 (continued)

Study	Regimen	Drugs	Common adverse events		% ≥VGPR
Gay et al., ASCO, 2017 and ASH, 2018 (n = 474), Phase III [16]	KRD	Carfilzomib 20/36 mg/m^2, d 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg/d, d 1–21 Dexamethasone 20 mg/d, d 1, 2, 8, 9, 15, 16 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	5% Not reported 1% 1%	74% after 4 cycles
	KCD	Carfilzomib 20/36 mg/m^2, d 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m^2, d 1–21 Dexamethasone 20 mg/d, d 1, 2, 8, 9, 15, 16 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	3% Not reported 0% 2%	61% after 4 cycles
Moreau et al., ASH, 2016 [14] (n = 42), Phase II	IRD	Ixazomib 4 mg/d, d 1, 8, 15 Lenalidomide 25 mg/d, d 1–21 Dexamethasone 40 mg/d, d 1, 8, 15, 22 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	19% 0% Not reported 2% (all ≥ III)	36% after 3 cycles
Moreau et al., Lancet, 2019 [17] (n = 1085), Phase III	VTD	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Cyclophosphamide 500 mg/m^2, d 1, 8, 15 po Dexamethasone 40 mg/d, d 1–4, 9–12 28-days-cycle	Neutropenia Lymphopenia Stomatitis Thrombopenia	15% 10% 16% 7%	78% after 6 cycles + ASCT
	VTD + Dara	VTD as above + Daratumumab (16 mg/kg IV QW C 1–2, Q2W C 3–6) Both arms 4 cycles before and 2 cycles after ASCT	Neutropenia Lymphopenia Stomatitis Thrombopenia	28% 17% 13% 11%	83% after 6 cycles + ASCT

Table 18.5 Mobilization strategies

Collection strategy	Agent	Advantage	Disadvantage
Growth factors alone	G-CSF (e.g., Neupogen®)	Moderate side effects [71] Cost-effective	Suboptimal in patients with risk factors for poor mobilization including lenalidomide pretreatment [26, 27, 72]
Chemo mobilization	G-CSF following chemotherapy	Higher cell yields than G-CSF alone [73–76]	Toxic side effects [73, 77–79] Not associated with better disease control [80, 81]
Chemokine receptor (CXCR4) antagonist	Plerixafor (Mozobil®)	Mobilization in patients with risk factors for poor mobilization [82–84] Rapid kinetics [85]	Higher costs

G-CSF granulocyte colony-stimulating factor

High-Dose Therapy

1. Melphalan 200 mg/m^2 is considered the standard of care [28] and usually administered intravenously in divided doses on days −3 and −2 or as a single dose on day −2 only before autoHCT.
   a. Dose reduction to 100 mg/m^2 is associated with an adverse outcome [29].
   b. To prevent anticipated toxicities in medically compromised patients (e.g., elderly patients or patients with cardiac disease), the melphalan dosage might be reduced to 140 mg/m^2 without apparent loss of efficacy compared to 200 mg/m^2 [30].
   c. Also in patients with renal insufficiency (RI) and dialysis-dependent renal impairment, melphalan should be reduced accordingly to obtain comparable results to patients with normal/mild RI and potentially achieve dialysis independence [31].
2. Tandem transplantation
   a. In the past, several studies addressed the question of whether a tandem autoHCT, that is, a second autoHCT usually within 6 months after the first, should be performed [32].
   b. In the era of novel agent-based induction and maintenance therapy, conflicting results from two prospective phase III trials have been reported.
      i. While the abovementioned EMN02/HO95 phase III trial demonstrated the inferiority of single versus tandem autoHCT [6], especially in patients with the high-risk disease [33], the StaMINA trial showed no significant differences for PFS and overall survival (OS) between single and tandem autoHCT, even in patients with the high-risk disease [34].

ii. In the author's practice, tandem autoHCT is offered to patients with the suboptimal response after induction therapy, FISH-based high-risk cytogenetics, or those patients not in complete remission after a first autoHCT.

Supportive Care

1. Patients with newly diagnosed MM are prone to infections due to the impaired humoral and cellular immunity caused by the proliferation of malignant plasma cells and the production of nonfunctional antibodies.
2. Infectious complications are the most common cause of death during the first 3 months of therapy, and one study suggested that antibiotic prophylaxis can reduce febrile episodes and death [35]. Table 18.6 summarizes the recommended prophylaxis.
3. General treatment of infectious complications such as neutropenic fever is discussed separately in this book. Furthermore, vaccinations need to be repeated after autoHCT, and one suggested schedule of administration is summarized in Table 18.7; an alternative schedule of administration is provided in Appendix 9.
4. Other common side effects of autoHCT for MM are nausea and vomiting as well as gastrointestinal mucositis.

Table 18.6 Summary of prophylaxis for most common transplant-related side effects

Infection prophylaxis				
Pathogen	Population	Drugs	Dosing	Timing
Bacterial	All newly diagnosed patients [35] Patients undergoing autoHCT	Levofloxacin	500 mg/d	12 weeks after initiating therapy until neutrophil recovery in autoHCT
Fungal	Patients undergoing autoHCT	Fluconazole	400 mg/d	d0–30 after autoHCT
Pneumocystis jirovecii	Patients undergoing autoHCT	Trimethoprim/ sulfamethoxazole	800/160 mg BID	d0–180 after autoHCT
Herpes simplex virus	Patients treated with proteasome inhibitors (PI) and/or monoclonal antibodies Patients undergoing autoHCT	Acyclovir	400 mg BID	Start and 3 weeks after PI d0–180 after CT

Table 18.6 (continued)

Infection prophylaxis				
Pathogen	Population	Drugs	Dosing	Timing
Varicella zoster virus	Patients treated with proteasome inhibitors (PI) Patients undergoing autoHCT	Acyclovir Inactivated-virus vaccine (Shingrix®)	400 mg BID	Start and 3 weeks after PI therapy d0–180 after autoHCT First dose 5–60 days before autoHCT Second/third doses at about 30, 60, and 90 days autoHCT [36]
Hepatitis B	All HBs-antigen and/or HBV DNA positive patients treated for MM patients including autoHCT	Lamivudine	100 mg/d	Start and 6 months after every MM therapy including autoHCT
Hepatitis C	All infected patients (hepatitis C RNA positive) should receive treatment	Prophylaxis not recommended		
Human immunodeficiency virus	All infected patients should receive highly active antiretroviral therapy	Prophylaxis not recommended		

Prophylaxis of other common side effects			
Side effect	Drug	Dosing	Comment
Nausea and vomiting	e.g., combination of		Improves nausea/vomiting and quality of life compared to granisetron and dexamethasone plus placebo [37]
	aprepitant	125 mg/d day 1; 80 mg/d days 2–4	
	granisetron	2 mg/d days 1–4	
	dexamethasone	4 mg/d day 1; 2 mg/d days 2–3	
Oral Mucositis	Palifermin (Kepivance®)	60 µg/kg/d Three doses before and three doses after ASCT	Improves quality of life, consider financial toxicity [38]
	Ice cubes	Oral administration during melphalan infusion	Reduces oral mucositis and febrile episodes without adding severe side effects or costs [39]
Prolonged neutropenia	Granulocyte-colony stimulating factor	50 µg/m^2/d day 1 after ASCT until ANC ≥ 500/µl	Associated with faster engraftment [40], might reduce mucositis and febrile neutropenia, might cause engraftment or capillary leakage syndrome. Cost-effectiveness uncertain [41]

Table 18.7 Vaccinations recommended after autoHCT for MM (Roswell Park Comprehensive Cancer Institute Guidelines)

Pathogen	First dose after autoHCT (months)	Time points
Influenza (inactivated)	6	Yearly during flu season
Polio (inactivated)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Pneumococcal (conjugate)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Hemophilus influenza B (conjugate)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Hepatitis A and B	6	3 doses, 1–3-month intervals
Meningococcal	6	2 doses, 6-month intervals
Diphtheria, acellular pertussis, and tetanus toxoids	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Measles, mumps, rubella (live)	24	2 doses, 2–3-month intervals
Varicella virus (live) or Shingrix®	24	2 doses, 2–3-month intervals

Maintenance Therapy After AutoHCT

Maintenance therapy in MM after autoHCT has been shown to improve OS. The commonly used agent is lenalidomide, whereas new approaches show also improved survival for maintenance therapy with bortezomib and ixazomib [3, 42–45].

1. Lenalidomide (Revlimid®)
    a. Lenalidomide is indicated as standard maintenance therapy after autoHCT in the United States and Europe.
    b. 4 randomized trials showed significantly improved PFS with lenalidomide maintenance therapy versus placebo or observation [3, 42–45].
    c. Meta-analyses demonstrated improved OS [45].
    d. Standard dosing: 10 mg po daily continuous, increase up to 15 mg daily if tolerated [45].
    e. Main side effects [46]
        i. Hematologic toxicity (neutropenia, anemia, thrombocytopenia)
        ii. Increased risk of secondary primary malignancies
        iii. Increased risk of venous thromboembolic events (VTE)
        iv. Gastrointestinal side effects (esp. diarrhea)
        v. Drug rash
    f. Concurrent medication [47, 48]:
        i. If no other risk factors for VTE: aspirin 81 mg/d po.
        ii. If other risk factors for VTE: low-molecular-weight heparin or full-dose warfarin.

iii. Oral anticoagulants such as apixaban (Eliquis®) were successfully evaluated for VTE prophylaxis in IMiD-treated patients [49].

g. Duration

i. Three out of the four randomized phase III studies involved continuing maintenance treatment until disease progression.
ii. Administration of lenalidomide beyond the achievement of complete remission (CR) is associated with better OS and therefore should be continued until disease progression if toxicities are tolerable [50].

2. Bortezomib (Velcade®)

a. Bortezomib with induction and maintenance improved PFS compared to vincristine with induction and thalidomide with maintenance [51, 52].
b. Improves outcome in patients with del(17p) [53].
c. Standard dosing: 1.3 mg/m^2 sc every 2 weeks [51].
d. Main side effects [54]:

i. Hematologic toxicity (neutropenia, thrombocytopenia)
ii. Peripheral neuropathy
iii. Gastrointestinal side effects

e. Concurrent medication:

i. Herpes zoster prophylaxis with low-dose acyclovir [55]

f. Duration: In studies discontinuation after 2 years [51]. Based on results from lenalidomide maintenance studies, treatment until progression might prolong survival and should be considered if no severe side effects occur.

3. Ixazomib (Ninlaro®)

a. Improved post-autoHCT PFS by 5 months when compared to placebo [70]
b. Standard dosing: 3 mg po every 2 weeks; may increase up to 4 mg if tolerated
c. Main side effects:

i. Hematologic toxicity (thrombocytopenia)
ii. Peripheral neuropathy
iii. Gastrointestinal side effects

d. Concurrent medication:

i. Herpes zoster prophylaxis with low-dose acyclovir.

e. Duration: In studies, discontinuation after 2 years. Based on results from lenalidomide maintenance studies, treatment until progression might prolong survival and should be considered if no severe side effects occur.

Table 18.8 Revised response criteria for minimal residual disease (MRD)

Response MRD	Response criteria
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells in the bone marrow by NGF with a minimum sensitivity of 1 in 10^5 nucleated cells
Sequencing MRD-negative	Absence of clonal plasma cells by NGS in the bone marrow by NGS with a minimum sensitivity of 1 in 10^5 nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus (a) Disappearance of increased tracer uptake found at baseline or preceding PET/CT or (b) Decrease to less mediastinal blood pool standardized uptake value (SUV) or (c) Decrease to less than that of surrounding normal tissue
Sustained MRD-negative	MRD negativity by NGF or NGS and in imaging for at least 1 year

NGF next-generation flow, *NGS* next-generation sequencing

Response Criteria

Historically, response criteria were based on the measurement of monoclonal protein in serum and urine as well as bone marrow plasma cell count. Response is categorized in stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD). Revised criteria include new parameters of minimal residual disease (MRD) measured by flow cytometry or gene sequencing (Table 18.8). Furthermore, sensitive imaging techniques can detect extramedullary residual disease [57].

Salvage AutoHCT

Retrospective analyses demonstrated that salvage autoHCT after re-induction therapy is an option for patients with relapsed disease, particularly those with sustained remission ≥18 months after a first autoHCT procedure [58, 59]. Currently, there are only two published prospective randomized phase III trials comparing salvage autoHCT after novel agent-based re-induction therapy to treatment with a novel agent alone in relapsed MM (Table 18.9) [60, 61]. While the study from the UK showed the superiority of salvage autoHCT over monotherapy with weekly cyclophosphamide, the German study could not show any differences in the intention-to-treat analysis. While major criticism of the study from the UK was the suboptimal control arm with weekly cyclophosphamide, the final analysis of the German study is still pending.

Table 18.9 Summary of current phase III trials for autoHCT for relapsed disease

Study	Arm	Re-induction		Consolidation	Maintenance	Common adverse events		Survival analysis
Cook et al., Lancet Oncol, 2014 [60] ($n = 297$)	autoHCT	PAd 4 cycles	Bortezomib 1.3 mg/m^2, d 1, 4, 8, 11 Doxorubicin 9 mg/m^2, d 1–4 Dexamethasone 40 mg/d, d 1–4, 9–12, 17–20 (from cycle 2: 40 mg/d, d 1–4) 28-days-cycle	High-dose melphalan 200 mg/m^2 followed by autoHCT (7% did not receive autoHCT)	No maintenance	Infections Neutropenia Thrombocytopenia Diarrhea	4% 75% 72% 12% (all ≥ II)	Intention to treat (ITT); autoHCT vs. cyclophosphamide: PFS: (19 vs. 11 mo; $p < 0.0001$) OS (67 vs. 52 mo; $p = 0.022$)
	Control			Cyclophosphamide 400 mg/m^2 PO weekly for 12 cycles	No maintenance	Infections Neutropenia Thrombocytopenia Diarrhea	0% 13% 4% 1% (all ≥ II)	
Goldschmidt et al., ASH, 2018 [61] ($n = 282$)	autoHCT	RD 3 cycles	Lenalidomide 25 mg/d, d 1–21 Dexamethasone 40 mg/d, d 1, 8, 15, 22 28-days-cycle	High-dose melphalan 200 mg/m^2 followed by autoHCT (30% did not receive autoHCT)	Lenalidomide 10 mg/d	Infections Neutropenia Thrombocytopenia Oral mucositis	33% 62% 45% 10% (all ≥°III)	ITT: autoHCT vs. RD until progression No significant PFS/OS differences Per protocol: PFS (23 vs 20 mo; $p = 0.09$) OS (not reached vs 57 mo; $p = 0.046$)
	Control			RD until progression	RD until progression	Infections Neutropenia Thrombocytopenia Oral mucositis	28% 25% 11% 2% (all ≥°III)	

Adoptive Cellular Therapies

1. Allogeneic transplantation (alloHCT)
   a. In contrast to autoHCT, alloHCT has the potential to generate an immunologic graft-versus-myeloma (GvM) effect.
      i. Studies comparing autoHCT and alloHCT as first-line therapy showed improved long-term OS for patients undergoing alloHCT, while transplant-related mortality (TRM) and toxicity mostly as a consequence of graft-versus-host disease (GvHD) were increased [62–65].
      ii. Whether alloHCTcan overcome high-risk disease features remains controversial since inclusion criteria for high-risk disease varied in the different studies [66–68].
      iii. As the incidence of TRM is 10–20%, alloHCT in MM should generally be reserved for young patients with primary relapsed/refractory disease, where transplant risk is relatively low (HLA-identical donor, no comorbidities) and no other novel therapy, for example, antibodies or chimeric antigen receptor T-cell is available.
   b. Studies comparing alloHCT to novel agents such as proteasome inhibitors, immunomodulatory agents, or monoclonal antibodies are lacking.
2. Chimeric antigen receptor T (CAR T) cell therapy
   a. CAR T cells are genetically engineered T cells utilizing a genetically engineered CAR targeting specific myeloma antigens, of which current studies are mainly directed against B-cell maturation antigen (BCMA).
   b. Phase I/II trials are presently investigating safety and efficacy for CAR T cell therapy for myeloma in heavily pretreated patients.
   c. Although overall response rates (ORR) up to 100% have been reported and the majority of patients achieved a VGPR or CR, long-term results have not been established to determine the durability of these responses [69].
   d. The observed toxicities of this therapy are similar to more established CAR T cell therapies in acute lymphoid leukemia (ALL) and aggressive lymphomas, most frequently grade 1–2 cytokine release syndrome (CRS) and neurotoxicity [69, 70].

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